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L9	L5 and (rapamycin or cyclosporin$ or ciclosporin$)	97	L9
	DB=PGPB; PLUR=YES; OP=ADJ		
L8	L5	130	L8
	DB=EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ		
L7	L5	3	L7
	DB=USPT; PLUR=YES; OP=ADJ		
L6	L5	84	L6
	DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ		
L5	(b7-1 or cd80)same(b7-2 or cd86)same(antibod$ or immunoglobulin$)same (combin$ or together or additive or synerg$)same (transplant$ or graft$)	217	L5

L4	(b7-1 or cd80)same(b7-2 or cd86)same(antibod$ or immunoglobulin$)same (combin$ or together or additive or synerg$) and (transplant$ or graft$)	447	L4
L3	L1 and cd40	6	L3
L2	L1 and (b7-1 or cd80)same(antibod$ or immunoglobulin$) and (b7-2 or cd86)same(antibod$ or immunoglobulin$)	7	L2
L1	co.in.	3691	L1

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US006280957B1

(12) **United States Patent**
Sayegh et al.

(10) **Patent No.: US 6,280,957 B1**
(45) **Date of Patent: Aug. 28, 2001**

(54) **COSTIMULATORY BLOCKADE AND MIXED CHIMERISM IN ALLO-TRANSPLANTATION**

(75) Inventors: **Mohamed Sayegh**, Westwood; **Megan Sykes**, Charlestown, both of MA (US)

(73) Assignee: **The General Hospital Corporation**, Charlestown, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/245,614**

(22) Filed: **Feb. 4, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/073,864, filed on Feb. 4, 1998.

(51) **Int. Cl.**[7] **G01N 33/53**; C12N 5/06; C07K 16/00; A61F 13/00

(52) **U.S. Cl.** **435/7.1**; 435/343.2; 530/388.75; 424/422

(58) **Field of Search** 435/7.1, 343.2; 530/388.75; 424/422

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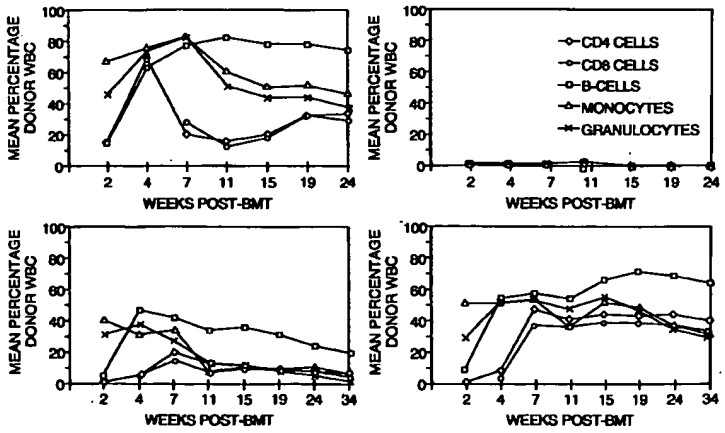
Primary Examiner—Hankyel T. Park
(74) *Attorney, Agent, or Firm*—Hale and Dorr LLP

(57) **ABSTRACT**

Use of the blockade of costimulation and hematopoietic stem cells in allograft transplantation.

13 Claims, 5 Drawing Sheets



US006709654B1

(12) **United States Patent**
Anderson et al.

(10) **Patent No.: US 6,709,654 B1**
(45) **Date of Patent: Mar. 23, 2004**

(54) **TREATMENT OF PSORIASIS USING ANTI-B7.1 (CD80) ANTIBODIES**

(76) Inventors: **Darrell R. Anderson**, 29246 Lawrence Welk La., Escondido, CA (US) 92029; **Peter Brams**, 4303 Proctor Pl., San Diego, CA (US) 92116; **Nabil Hanna**, 16016 Camino Deliciada, Rancho Santa Fe, CA (US) 92067; **William S. Shestowsky**, 1155 Thomas Ave., San Diego, CA (US) 92109; **Cheryl Heard**, 1225 Via Montoro, Encinitas, CA (US) 92024

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/383,916**

(22) Filed: **Aug. 26, 1999**

Related U.S. Application Data

(62) Division of application No. 08/487,550, filed on Jun. 7, 1995, now Pat. No. 6,113,898.

(51) **Int. Cl.**[7] **A61K 39/395**; C07K 16/28

(52) **U.S. Cl.** **424/153.1**; 424/130.1; 424/141.1; 424/143.1; 424/144.1; 424/154.1; 424/173.1; 530/387.1; 530/388.1; 530/388.2; 530/388.22; 530/388.7; 530/388.73; 530/388.75

(58) **Field of Search** 424/130.1, 141.1, 424/153.1; 530/387.1, 388.22, 388.75

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Primary Examiner—Phillip Gambel

(57) **ABSTRACT**

The present invention relates to the identification of macaque antibodies to human B7.1 and B7.2 by screening of phage display libraries or monkey heterohybridomas obtained using B lymphocytes from B7.1 and/or B7.2 immunized monkeys. More specifically, the invention provides four monkey monoclonal antibodies 7B6, 16C10, 7C10 and 20C9 which inhibit the B7:CD28 pathway and thereby function as effective immunosuppressants. The invention further provides the complete DNA and amino acid sequences of the light and heavy chain of three primatized antibodies derived from those monkey monoclonal antibodies which bind B7.1 and possibly B7.2, primatized 7C10, primatized 7B6 and primatized 16C10. These primatized and monkey antibodies may be used as specific immunosuppressants, e.g., for the treatment of autoimmune diseases and to prevent organ transplant rejection.

7 Claims, 22 Drawing Sheets

US006719972B1

(12) **United States Patent**
Gribben et al.

(10) **Patent No.: US 6,719,972 B1**
(45) **Date of Patent: *Apr. 13, 2004**

(54) **METHODS OF INHIBITING T CELL PROLIFERATION OR IL-2 ACCUMULATION WITH CTLA4- SPECIFIC ANTIBODIES**

(75) Inventors: **John G. Gribben**, Brookline, MA (US); **Gordon J. Freeman**, Brookline, MA (US); **Lee M. Nadler**, Newton, MA (US); **Paul Rennert**, Holliston, MA (US); **Cindy L. Jellis**, Londonderry, NH (US); **Edward Greenfield**, Randolph, MA (US); **Gary S. Gray**, Brookline, MA (US)

(73) Assignees: **Repligen Corporation**, Cambridge, MA (US); **Dana-Farber Cancer Institute**, Boston, MA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/253,783**

(22) Filed: **Jun. 3, 1994**

(51) **Int. Cl.**[7] **A61K 39/395**; C07K 16/28

(52) **U.S. Cl.** **424/154.1**; 424/130.1; 424/133.1; 424/134.1; 424/139.1; 424/141.1; 424/143.1; 424/144.1; 424/145.1; 424/153.1; 424/173.1; 530/387.1; 530/387.3; 530/387.9; 530/388.1; 530/388.2; 530/388.22; 530/388.7; 530/388.73; 530/388.75

(58) **Field of Search** 514/2; 424/130.1, 424/134.1, 143.1, 145.1, 133.1, 141.1, 158.1; 530/387.1, 388.22, 388.8, 388.23, 388.75

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Primary Examiner—Phillip Gambel
(74) *Attorney, Agent, or Firm*—Lahive & Cockfield, LLP; Amy E. Mandragouras, Esq.; DeAnn F. Smith, Esq.

(57) **ABSTRACT**

Isolated ligands which bind a molecule expressed on the surface of T cells and induce antigen specific apoptosis in activated T cells are disclosed. Preferably, the T cell surface molecule is CTLA4 and the ligand is a monoclonal anti-CTLA4 antibody that binds to an epitope of CTLA4 distinct from the binding sites of B7-1 and B7-2. Upon binding of the antibody to CTLA4 on an activated T cell, in the presence of an antigenic signal, antigen specific apoptosis is induced. The invention also describes a novel natural CTLA4 ligand, distinct from B7-1 and B7-2, which mediates induction of apoptosis. Pharmaceutical compositions of anti-CTLA4 antibodies or other isolated CTLA4 ligands which can be administered to subjects to induce T cell apoptosis, thereby clonally deleting antigen specific. T cells, such as alloreactive T cells in transplantation situations or autoreactive T cells in autoimmune disorders, are also disclosed. Methods for inducing T cell apoptosis in vitro with an anti-CTLA4 antibody or other ligand of the invention together with an antigen specific signal are also disclosed, e.g., for use in purging alloreactive T cells from donor bone marrow prior to bone marrow transplantation to inhibit graft versus host disease.

11 Claims, 2 Drawing Sheets

US006984383B1

(12) **United States Patent**
Co et al.

(10) **Patent No.: US 6,984,383 B1**
(45) **Date of Patent: Jan. 10, 2006**

(54) **METHOD OF TRANSPLANTING CELLS BY CONTACTING DONOR CELLS WITH B7-1-AND B7-2-SPECIFIC IMMUNOGLOBULINS**

(75) Inventors: **Man Sung Co**, Cupertino, CA (US); **Maximiliano Vasquez**, Palo Alto, CA (US); **Beatriz Carreno**, Acton, MA (US); **Abbie Cheryl Celniker**, Newton, MA (US); **Mary Collins**, Natick, MA (US); **Samuel Goldman**, Acton, MA (US); **Gary S. Gray**, Brookline, MA (US); **Andrea Knight**, Hampton, NH (US); **Denise O'Hara**, Reading, MA (US); **Bonita Rup**, Reading, MA (US); **Geertruida M. Veldman**, Sudbury, MA (US)

(73) Assignee: **Genetics Institute, LLC**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/626,731**

(22) Filed: **Jul. 27, 2000**

Related U.S. Application Data

(62) Division of application No. 09/249,011, filed on Feb. 12, 1999.

(51) **Int. Cl.**

A61K 39/395	(2006.01)
A61K 35/26	(2006.01)
A61K 35/28	(2006.01)
C07K 16/28	(2006.01)

(52) **U.S. Cl.** **424/153.1**; 424/130.1; 424/133.1; 424/140.1; 424/141.1; 424/143.1; 424/144.1; 424/173.1; 424/93.7; 424/93.71; 424/577; 424/578; 530/387.1; 530/387.3; 530/388.1; 530/388.2; 530/388.22; 530/388.7; 530/388.73

(58) **Field of Classification Search** 424/130.1, 424/133.1, 143.1, 173.1, 577; 530/387.1, 530/388.2, 388.73

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to a humanized anti-B7-2 antibody that comprises a variable region of nonhuman origin and at least a portion of an immunoglobulin of human origin. The invention also pertains to methods of treatment for various autoimmune diseases, transplant rejection, inflammatory disorders and infectious diseases by administering humanized anti-B7-2 and/or anti-B7-1 antibodies.

18 Claims, 12 Drawing Sheets

US006576236B1

(12) **United States Patent**
Boussiotis et al.

(10) **Patent No.: US 6,576,236 B1**
(45) **Date of Patent: Jun. 10, 2003**

(54) **METHODS FOR STIMULATING T CELL RESPONSES BY MANIPULATING A COMMON CYTOKINE RECEPTOR γ CHAIN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/270,152**

(22) Filed: **Jul. 1, 1994**

(51) **Int. Cl.**[7] **A61K 39/395**; C07K 16/28

(52) **U.S. Cl.** **424/154.1**; 424/130.1; 424/141.1; 424/143.1; 424/144.1; 424/153.1; 424/154.1; 424/173.1; 530/387.1; 530/388.1; 530/388.2; 530/388.22; 530/388.7; 530/388.73; 530/388.75; 530/389.1; 530/389.6

(58) **Field of Search** 424/130.1, 141.1, 424/143.1, 154.1, 173.1, 153.1; 514/2, 8; 530/351, 388.22, 388.75, 387.1

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(57) **ABSTRACT**

When stimulated through the T cell receptor(TCR)/CD3 complex without requisite costimulation through the CD28/B7 interaction, T cells enter a state of antigen specific unresponsiveness or anergy. This invention is based, at least in part, on the discovery that signaling though a common cytokine receptor γ chain (e.g., interleukin-2 receptor, interleukin-4 receptor, interleukin-7 receptor) prevents the induction of T cell anergy. This γ chain has been found to be associated with a JAK kinase having a molecular weight of about 116 kD (as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis) and signaling through the γ chain induces phosphorylation of the JAK kinase. Accordingly, methods for stimulating or inhibiting proliferation by a T cell which expresses a cytokine receptor γ chain are disclosed.

11 Claims, 4 Drawing Sheets

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 14/705, 16/28, A61K 39/395, 38/17 — A1

(11) International Publication Number: WO 95/33770

(43) International Publication Date: 14 December 1995 (14.12.95)

(21) International Application Number: PCT/US95/06726

(22) International Filing Date: 2 June 1995 (02.06.95)

(30) Priority Data:
08/253,783 3 June 1994 (03.06.94) US

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(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
With amended claims.

(54) Title: LIGANDS FOR INDUCTION OF ANTIGEN SPECIFIC APOPTOSIS IN T CELLS

(57) Abstract

Isolated ligands which bind a molecule expressed on the surface of T cells and induce antigen specific apoptosis in activated T cells are disclosed. Preferably, the T cell surface molecule is CTLA4 and the ligand is a monoclonal anti-CTLA4 antibody that binds to an epitope of CTLA4 distinct from the binding sites of B7-1 and B7-2. Upon binding of the antibody to CTLA4 on an activated T cell, in the presence of an antigenic signal, antigen specific apoptosis is induced. The invention also describes a novel natural CTLA4 ligand, distinct from B7-1 and B7-2, which mediates induction of apoptosis. Pharmaceutical compositions of anti-CTLA4 antibodies or other isolated CTLA4 ligands which can be administered to subjects to induce T cell apoptosis, thereby clonally deleting antigen specific T cells, such as alloreactive T cells in transplantation situations or autoreactive T cells in autoimmune disorders, are also disclosed. Methods for inducing T cell apoptosis *in vitro* with an anti-CTLA4 antibody or other ligand of the invention together with an antigen specific signal are also disclosed, e.g., for use in purging alloreactive T cells from donor bone marrow prior to bone marrow transplantation to inhibit graft versus host disease.